

**Notice of Allowability****Application No.**

10/524,547

**Applicant(s)**

KAPLAN ET AL.

**Examiner**

MAURY AUDET

**Art Unit**

1654

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 11/17/10.
2. ☒ The allowed claim(s) is/are 1 and 3-6.
3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some\* c) ☐ None of the:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.  
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
- (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
- 1) ☐ hereto or 2) ☐ to Paper No./Mail Date \_\_\_\_.
- (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08),  
Paper No./Mail Date \_\_\_\_
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413),  
Paper No./Mail Date 12/20/2010.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other \_\_\_\_.

/Maury Audet/  
Primary Examiner, Art Unit 1654

### **EXAMINER'S AMENDMENT**

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Adrian Kaplan, Applicant's Representative, on 12/20/10 (in order to provide antecedent basis for claim 3 back to the description, where the claims are read in light thereof; this limitation filed originally only present in the originally filed claims).

### **IN THE SPECIFICATION**

On page 6, line 11, after the term "vacuum", , the following phrase has been inserted:

--at a temperature in the range of about **40°C to about 150°C** --

### **Reasons for Allowance**

The following is an examiner's statement of reasons for allowance:

Claims 1 and 3-6, as drawn to a method of glyccating a protein comprising placing a lyophilized sample under vacuum and then heating the same under vacuum was not found to be reasonably taught or suggested by the prior art of record.

Also glycation of proteins is well known in the art (see Applicant's own background discussion; Ledl et al. Angew Chem. Int. Ed. Engl. (June 1990), 29(6), 565-594 - cited on this Form 892), there was no suggestion or motivation to apply the two vacuum steps, the latter including heating, in succession with the unexpected results therefrom.

As Applicant describes in the specification:

[0061]

The accepted mechanism for the glycation in water involves the nucleophilic attack of a protein's amino group on the open chain form of the reducing sugar forming a Schiff base which undergoes Amadori rearrangement to form the ketoamine derivative. As lysine  $\epsilon$ -amino groups in proteins normally have ionization constants of 10.5 to 11, very little glycation of amino groups would be expected below pH 10.5 where the protonated form of the amino group predominates. However, the results in Figure 3 show that the protonated form of the amino group is readily glycosylated by the *in vacuo* procedure. The mechanism by which this glycation occurs has not been established but it is clearly different from that postulated for glycation in solution.

Then back at the outset:

[0003]...

None of these studies have used a vacuum to promote the glycation reaction by the removal of water or to prevent the formation of advanced glycation end products.

[0004] Amino groups in dry proteins are present in their protonated form, and for glycation to take place, the reaction would have to involve these protonated amino groups. On the basis of current theory, a protonated amino group in solution does not react with the aldehyde form of a reducing sugar. Furthermore, there is no known theory that predicts that if a mixture of a protein and reducing sugar in the dry state were subjected to a vacuum that a water-stable glycosylated derivative would be formed. The fact that extensive

glycation of proteins does occur in the lyophilized state under vacuum with heating demonstrates that the protonated amino group does indeed react.

Therefore, there are two novel theoretical features to the discovery that lyophilized proteins can be efficiently glycosylated in vacuo in the dry state: 1.

A protonated amino group will react with a sugar aldehyde group in vacuo. 2.

A ketoamine derivative is formed which does not rapidly revert to the free amine and sugar when placed in aqueous solution.

As Applicant argued in the last response:

The Examiner agrees that Brodsky et al. does not use lyophilisation (vacuum) to achieve glycation. Tarelli et al. cited by the Examiner also used lyophilisation to remove water. Lyophilisation under vacuum is a standard procedure only for removing water from dissolved solutes and is particularly useful for drying solutions of proteins. There is not a single citation in the literature which claims that proteins can be glycosylated with the resultant formation of a ketoamine linkage by incubation at elevated temperature under vacuum, as now claimed in claim 1 as amended, of the present patent application.

Evidence that lyophilization of proteins for the production of glycosylated proteins is not obvious can be inferred by reference to the following recent treatise on the subject of protein lyophilisation: Cryopreservation and Freeze Drying Protocols, Second Edition, by John G. Gay and Glyn N. Stacey, In Methods in Molecular Biology, Volume 368, Humana Press, 2007. In this exhaustive treatise there is no mention or inference of using protein lyophilisation as a procedure, or as part of a procedure, for the glycation of proteins.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

### **Conclusion**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 12/20/2010

/Maury Audet/  
Primary Examiner, Art Unit 1654